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Evaluation of a standardised procedure to assess the shape of pellets using image analysis

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Abstract

The influence of threshold definition, number of pellets counted, image magnification and lightning technique on the assessment of pellet shape has been investigated using three batches of pellets and an image analysis system. The pellet parameters measured were 'aspect ratio', 'circularity', 'projection sphericity', '*e*R' and 'Feret diameter.' The methodical error, reproducibility and repeatability of the results were chosen as statistical test parameters. The position of the light source is crucial in providing an accurate particle size value. Top light was identified as the illumination technique that gave a mean pellet size similar to the true pellet size. The use of a light table produced significantly larger pellet size values. A minimum pixel resolution appears necessary for an accurate shape parameter definition. One pixel should not cover more than 30 μ m for pellets of an average particle size of 1.2 mm. Shape descriptors, which are based on a multiple combination of area and perimeter data such as the circularity, are greatly dependent on the number of pellets counted. Shape factors, which do not (aspect ratio) or only as a single value do involve an area or perimeter measurement $(e_R,$ projection sphericity) are, however, nearly independent of the number of pellets counted, as long as the magnification is sufficiently large and the pellets are randomly drawn from the batch. For nearly spherical particles, the methodical error is below 1%, but for elongated particles this error can reach 5%. The repeatability is also very good for nearly spherical particles ($\langle 2\%$), but increases to very large values if the particles are clearly elongated. The limiting values for the various shape factors should be reconsidered. An upper value for the aspect ratio of 1.1 and a lower value of 0.6 for e_R are recommended. The circularity should not be used as the shape factor to characterise spheres, because errors in image recognition can affect strongly the applicability of this shape factor. The projection sphericity has only a limited sensitivity to variations in particle shape. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: Pellet shape; Image analysis; Lightning technique; Image magnification; Threshold definition

1. Introduction

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Pellets are increasingly used to provide controlled-release dosage forms. For this purpose, they are either filled into hard gelatine capsules,

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or they are compacted into tablets. For the latter, the importance of particle shape has not yet been investigated, because the pellet strength is certainly the more dominant factor for the success of the final dosage form (Lundqvist et al., 1997, 1998; Salako et al., 1998). The filling of pellets into hard gelatine capsules appears generally possible as long as the pellets approach an aspect ratio below 1.2 and do not show large amounts of surface irregularities (Chopra et al., 1998).

In recent years, the use of image analysis has become the most common analytical procedure to evaluate the size and shape of pellets. Naturally, a large variety of equipment, test procedures and philosophies has appeared in the literature. A study on the validation of a computerised image analysis system (Zingerman et al., 1992) indicated that it would be difficult to compare results from different research groups because of the variety of variables involved.

The image analysis systems used to measure pellet shape are first different in basic assessment parameters. For example, the system used by Podczeck and Newton (1994) defines the different length parameters of a particle from 36 calliper measurements around each single two-dimensional pellet outline, i.e. using an angle of 5° rotation. In contrast, the system used by Lindner and Kleinebudde (1993) evaluates only eight calliper measurements employing an angle of rotation of 20° to define these length parameters. The precision of the determination of the 'maximum length' of the pellets appears reasonably accurate already for four calliper measurements. However, the 'minimum length', which is required to define the 'elongation' of the particle (Tsubaki and Jimbo, 1979) and, in some image analysis systems, to define the 'aspect ratio' (McCarthy, 1976), is significantly dependent on the number of calliper traces (Allen, 1997). The silhouette of a particle can be sufficiently reproduced from calliper traces 10° or less apart (Hawkins, 1993). Hence, the accuracy of shape factors such as the 'circularity' (Cox, 1927; Hausner, 1966) or the 'projection sphericity' (Pentland, 1927; Riley, 1941), which rely on either the assessment of the perimeter or the area of the two-dimensional particle outline, will also depend on the number of calliper traces around the silhouette. The smaller the number of traces, the less accurately these parameters are evaluated.

Pellets are three-dimensional, roundish objects, but their image is captured as a two-dimensional particle outline. It is impossible to focus precisely on the particle equator, because the equator is halfway down the pellet body. Also, image analysers compare several focal planes before the sharpest image (i.e. focus on the top of the spheres rather than the perimeter) is selected (Allen, 1997). Therefore, the captured image appears always slightly blurred around the pellet perimeter. An image camera provides a picture of pixels, which are arranged in horizontal and vertical lines. Hence, a circle is reproduced from a set of squares, i.e. an inherent source of error is always present. Also, the use of light tables causes shadows, which can add to the dark particle outline of the pellets. For this reason, Podczeck and Newton (1995) used a dark-field illumination technique with the light beam shining from the top of the image camera down onto the pellets. Here, the image is white, while the dark shadows add to the dark background only.

Different shape factors and shape assessment techniques are clearly different in their sensitivity to small variations in particle shape (Podczeck and Newton, 1994; Eriksson et al., 1997). Therefore, authors have adopted different opinions on the usefulness of shape factors. For example, Lindner and Kleinebudde (1993) considered the possibility of a quick assessment of a large number of pellets with a minimum of operator effort being the most important criterion. Yliruusi et al. (1992) tried to compensate for the lack in sensitivity of some shape factors by using a series of 20 shape descriptors in parallel, filtering the information by means of statistical analysis. Podczeck and Newton (1994, 1995) developed a shape factor (e_B) for two- or three-dimensional pellet shape assessment, which was shown to be significantly more sensitive to deviations from the ideal round shape and to surface irregularities than the standard shape factors used. However, its use, in particular the three-dimensional version of the shape factor, slows the assessment procedure down, and the raw data, which can principally be

obtained on any image analysis system, needs to be processed further.

Some image processing methods have also been described that are restricted to the functionality of the equipment. For example, Lindner and Kleinebudde (1993) employed a combined erosion and dilation cycle to separate touching pellet outlines. Most image analysers can erode and dilate images, but to achieve finally a particle shape identical with the original particle shape, the processed image and the original image have to be combined using Boolean algebra. The latter is not a standard feature of image analysis equipment, and external processing cannot compensate in this case.

Work in our laboratories revealed an operatordependent influence on pellet shape data, even when using identical equipment. A preliminary study pointed to the resolution that had been chosen, the subjectivity in setting the 'correct' threshold level and the position of the light source, as major influence factors. The number of pellets counted might also be involved. The aim of this study was to quantify the error produced and to design a standard operating procedure, which will assure comparable results in future work. It should be pointed out that some points studied, i.e. the resolution and the influence of threshold level, are primarily image analysis system dependent. However, other factors (illumination technique, number of pellets counted), the method of error evaluation as such and the main conclusions drawn, can be transferred to other image analysis systems in order to work out similar procedures. It is hoped that this will gradually lead to a harmonisation of image procedures between different research groups. Hence, comparison of results between laboratories could be improved.

2. Materials and methods

².1. *Materials*

Three batches of pellets were prepared by extrusion/spheronisation, varying the proposed particle shape by changes in the formula used. Details of the composition and process variables have been described earlier (Chopra et al., 1998). Two of the batches ('GR' and 'AL') contained visibly round pellets, while the third batch was composed of elongated cylindrical pellets ('CY'). All batches were size classified, and only the sieve fraction -1.4 to $+1.0$ mm was used in this study.

².2. *Methods*

The determination of the particle size (Feret diameter) and the particle shape (aspect ratio, circularity, projection sphericity, e_R) was carried out using the following Image Analysis system: 'Sonata' (Seescan, Cambridge, UK), equipped with a black/white camera (CCD–4 miniature video camera module; Rengo Co. Ltd., Toyohashi, Japan) and a zoom lens (18–108/2.5; Olympus Co. Europe, Hamburg, Germany). A cold light source (Type FLQ 85E; Olympus Co. Europe) was used in top and side light position to illuminate the pellets against a dark surface, whereas a light table (Type LV 28; P. W. Allen & Co., London, UK) was used for illumination from below.

The Feret diameter of a pellet is here defined as the average calliper distance of 36 measurements around the particle employing a 5° angle of rotation. In agreement with Schneiderhöhn (1954), the aspect ratio (AR) of each individual particle is the ratio between the longest calliper distance and the calliper distance perpendicular to the longest one. The circularity (*C*) was calculated from Cox (1927):

$$
C = \frac{4\pi A}{P^2} \tag{1}
$$

where *A* is the projected area of the two-dimensional particle outline, and *P* is the perimeter of this outline. The projection sphericity (PS) was first defined by Pentland (1927) as follows:

$$
PS = \frac{4A}{\pi d_L^2} \tag{2}
$$

where d_{L} is the longest calliper distance observed when tracing around the particle. The shape factor e_R was introduced by Podczeck and Newton (1994, 1995) as:

$$
e_{\mathbf{R}} = \frac{2\pi}{P} \frac{r_{\mathbf{e}}}{f} - \sqrt{1 - \left(\frac{b}{l}\right)^2} \tag{3}
$$

where r_e is a mean radius derived here from 72 distance measurements between the centre of gravity of the two-dimensional particle outline and the perimeter, using an angle of rotation of 5° between each line. The values of *b* and *l* are the length and the breadth of the two-dimensional particle outline, respectively, assuming a round $(b = l)$ or elliptical $(b < l)$ shape of the pellets. The value *f* is a correction factor (Podczeck and Newton, 1995):

$$
f = 1.008 - 0.231 \left(1 - \frac{b}{l} \right)
$$
 (4)

All four shape factor values and the Feret diameter can be measured simultaneously for each particle. The memory capacity of the image analyser allows the storage and processing of up to 800 particle data under these conditions. In those cases, where more than 800 particles are to be assessed, the rules of additivity for the arithmetic mean value and the variance (Snedecor and Cochran, 1980) were exploited.

A stereo–microscope (Olympus BH-2; Olympus Co., Tokyo, Japan) was used to measure the size of individual pellets with transmission light. The microscope was calibrated with a transmission graticule (CS 809; Graticule Ltd., Tonbridge, UK).

3. Results and discussion

3.1. *Accuracy of image thresholds*

Image analysis converts the optical picture of an object and its surroundings into a set of pixels to which different grey values are assigned. To process such an image, the operator must select the grey values which belong to the object, thereby discarding all pixels with grey values below or above an upper and/or lower threshold. The accuracy with which the threshold grey values can be chosen depends on the contrast and the sharpness of the picture. Images of pellets can be obtained as sharp pictures, but the grey values along the perimeter of the particle outlines are often blurred due to the perimeter being outside the focus plane. Bearing this in mind, the British Standard Committee has suggested that image analysis procedures should be accurate with respect to the "setting of a true threshold level $+5$ units''. However, a 'true threshold level' cannot exist, because this value depends strongly on the illumination technique employed. Hence, the definition of a useful threshold value for large objects such as pellets will experience an operator dependence. A standard operating procedure must, therefore, include a set-up procedure for the appropriate threshold level.

To study the influence of the threshold level on the pellet shape, only 10 pellets were used at a time. The number was restricted so that the pellets could remain in the counting field at exactly the same position during all tests. These tests involved seven different magnifications for pellet batch GR, and always one magnification for batches AL and CY. Images were taken at a given magnification and thresholded to an operator-dependent optimal threshold level. The pellet properties were then measured. Afterwards, the threshold level was increased or decreased by one unit, and the measurement was repeated. The best operatorindependent threshold level was then defined as the value providing an average pellet shape of the 10 pellets, which indicated 'best roundness'. The results are summarised in Table 1.

The aspect ratio and the projection sphericity are comparatively insensitive to a change in the threshold value by one unit. For nearly round pellets, the maximum change observed over a change of five units is 0.02 for the aspect ratio and 0.03 for the projection sphericity. However, the shape factor e_R clearly depends on the threshold value. In some circumstances (e.g. experiment GR/25.74/threshold values 11 and 12, see Table 1) the change in shape factor obtained is statistically significant (*t*-test, $t = 2.73$, $P < 0.05$). The value of this shape factor depends to a greater extent on the accuracy of the definition of the edges of the particle outline, because here, in addition to the perimeter of the particle outline, a number of distances from the centre of gravity to the perimeter are measured. Over- or under-thresholding of images leads primarily to 'rough' particle outlines,

which are then interpreted as surface irregularities when evaluating e_{R} .

When using non-spherical pellets (batch CY, see Table 1), the aspect ratio also became more dependent on the correct setting of the threshold value. Hence, regardless of the shape factor used in an experiment, a standardised procedure to set up the threshold level appears important if comparisons between different batches are to be made.

For all further experiments, the following standard routine was employed to avoid larger deviations in the shape factor due to threshold inconsistencies. From the number of pellets to be measured, 10 pellets were randomly drawn and positioned in the field of view. After adjustment

Table 1

Influence of the threshold value on the shape of pellets using image analysis	
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* Best threshold value.

Table 2

Arithmetic mean and standard deviation of various shape factors studied at different magnifications (i.e. pixel heights) and counting different numbers of pellets using batch GR

Pixel height (μm)	Number of pellets	Aspect ratio	Circularity	e_{R}	Projected sphericity
20.34	10	1.09 ± 0.07	0.83 ± 0.01	0.58 ± 0.15	0.86 ± 0.05
	25	1.10 ± 0.06	0.84 ± 0.05	0.55 ± 0.13	0.85 ± 0.06
	50	1.10 ± 0.06	0.86 ± 0.05	0.56 ± 0.13	0.85 ± 0.05
	100	1.09 ± 0.06	$0.87 + 0.05$	0.57 ± 0.12	0.86 ± 0.05
	250	1.09 ± 0.06	0.88 ± 0.05	0.58 ± 0.12	0.86 ± 0.05
	500	1.09 ± 0.06	0.89 ± 0.05	0.58 ± 0.12	0.86 ± 0.05
	1000	1.10 ± 0.06	0.89 ± 0.05	0.58 ± 0.11	0.86 ± 0.05
25.74	10	1.09 ± 0.06	0.90 ± 0.03	0.60 ± 0.13	0.87 ± 0.04
	25	1.10 ± 0.07	0.92 ± 0.05	0.58 ± 0.12	0.87 ± 0.05
	50	1.10 ± 0.07	0.84 ± 0.10	0.54 ± 0.12	0.86 ± 0.05
	100	1.10 ± 0.07	$0.85 + 0.09$	0.55 ± 0.12	0.86 ± 0.05
	250	1.09 ± 0.06	0.89 ± 0.07	0.58 ± 0.13	0.87 ± 0.05
	500	1.09 ± 0.06	0.90 ± 0.06	0.59 ± 0.12	0.87 ± 0.04
	1000	1.09 ± 0.06	0.90 ± 0.05	0.59 ± 0.12	0.87 ± 0.04
29.99	10	1.06 ± 0.02	0.94 ± 0.01	0.65 ± 0.06	0.89 ± 0.02
	25	1.08 ± 0.04	0.92 ± 0.02	0.60 ± 0.08	0.88 ± 0.03
	50	1.09 ± 0.04	0.90 ± 0.03	0.59 ± 0.09	0.87 ± 0.04
	100	1.08 ± 0.05	0.94 ± 0.04	0.62 ± 0.11	0.88 ± 0.04
	250	1.09 ± 0.05	0.92 ± 0.04	0.61 ± 0.11	0.88 ± 0.04
	500	1.09 ± 0.05	0.92 ± 0.04	0.61 ± 0.11	0.88 ± 0.04
	1000	1.09 ± 0.06	0.92 ± 0.04	0.60 ± 0.11	0.87 ± 0.04
34.63	10	1.11 ± 0.05	0.90 ± 0.02	0.54 ± 0.07	0.85 ± 0.05
	25	1.10 ± 0.06	0.91 ± 0.02	0.59 ± 0.12	0.86 ± 0.05
	50	1.09 ± 0.06	0.91 ± 0.02	0.60 ± 0.12	0.86 ± 0.04
	100	1.09 ± 0.06	0.91 ± 0.02	0.60 ± 0.12	0.87 ± 0.04
	250	1.09 ± 0.06	0.92 ± 0.03	0.60 ± 0.11	0.87 ± 0.04
	500	1.09 ± 0.06	0.92 ± 0.03	0.60 ± 0.11	0.87 ± 0.04
	1000	1.09 ± 0.06	0.91 ± 0.03	0.60 ± 0.11	0.87 ± 0.04
40.13	10	1.05 ± 0.04	0.93 ± 0.01	0.69 ± 0.10	0.88 ± 0.03
	25	1.06 ± 0.05	0.93 ± 0.01	0.67 ± 0.11	0.89 ± 0.03
	50	1.08 ± 0.05	0.93 ± 0.01	0.70 ± 0.11	0.88 ± 0.03
	100	1.08 ± 0.06	0.93 ± 0.01	0.63 ± 0.11	0.88 ± 0.04
	250	1.10 ± 0.06	0.93 ± 0.02	0.59 ± 0.11	0.86 ± 0.04
	500	1.10 ± 0.06	0.92 ± 0.02	0.59 ± 0.11	0.86 ± 0.04
	1000	1.09 ± 0.06	0.92 ± 0.02	0.60 ± 0.11	0.86 ± 0.04
61.70	10	1.06 ± 0.02	0.93 ± 0.01	0.65 ± 0.05	0.88 ± 0.03
	25	1.07 ± 0.05	0.94 ± 0.01	0.64 ± 0.10	0.87 ± 0.04
	50	1.09 ± 0.05	0.93 ± 0.02	0.62 ± 0.10	0.86 ± 0.04
	100	1.09 ± 0.06	0.93 ± 0.02	0.62 ± 0.11	0.86 ± 0.04
	250	1.10 ± 0.06	0.92 ± 0.02	0.60 ± 0.11	0.85 ± 0.04
	500	1.09 ± 0.06	0.92 ± 0.02	0.60 ± 0.11	0.86 ± 0.04
	1000	1.09 ± 0.06	0.92 ± 0.02	0.60 ± 0.11	0.86 ± 0.04
100.1	10	1.08 ± 0.04	0.93 ± 0.01	0.64 ± 0.09	0.86 ± 0.03
	25	1.10 ± 0.07	0.94 ± 0.01	0.61 ± 0.12	0.84 ± 0.04
	50				
	100	1.09 ± 0.05	0.93 ± 0.02	0.62 ± 0.11	0.85 ± 0.04
		1.09 ± 0.06	0.94 ± 0.02	0.62 ± 0.12	0.85 ± 0.04
	250	1.10 ± 0.07	0.94 ± 0.02	0.61 ± 0.12	0.84 ± 0.04
	500	1.10 ± 0.06	0.93 ± 0.02	0.61 ± 0.12	0.84 ± 0.04
	1000	1.09 ± 0.06	0.94 ± 0.02	0.62 ± 0.11	0.84 ± 0.04

Table 3

Arithmetic mean and standard deviation of various shape factors studied at different magnifications (i.e. pixel heights) and counting different numbers of pellets using batch AL

Pixel height (μm)	Number of pellets	Aspect ratio	Circularity	e_{R}	Projected sphericity
20.34	10	1.08 ± 0.08	0.87 ± 0.03	0.60 ± 0.14	0.89 ± 0.06
	25	1.08 ± 0.06	0.88 ± 0.02	0.60 ± 0.12	0.89 ± 0.04
	50	1.09 ± 0.06	0.88 ± 0.03	0.59 ± 0.11	0.88 ± 0.04
	100	1.08 ± 0.05	0.89 ± 0.03	0.60 ± 0.10	0.89 ± 0.04
	250	1.08 ± 0.05	0.89 ± 0.03	0.60 ± 0.10	0.89 ± 0.04
	500	1.08 ± 0.05	0.90 ± 0.03	0.60 ± 0.10	0.89 ± 0.04
	1000	1.08 ± 0.05	0.90 ± 0.03	0.61 ± 0.10	0.89 ± 0.04
25.74	10	1.06 ± 0.02	0.93 ± 0.01	0.67 ± 0.08	0.91 ± 0.02
	25	1.06 ± 0.04	0.92 ± 0.02	0.65 ± 0.09	0.90 ± 0.03
	50	1.06 ± 0.04	0.92 ± 0.03	0.66 ± 0.11	0.90 ± 0.03
	100	1.07 ± 0.04	0.91 ± 0.04	0.64 ± 0.10	0.89 ± 0.03
	250	1.07 ± 0.04	0.90 ± 0.03	0.63 ± 0.10	0.89 ± 0.03
	500	1.07 ± 0.04	0.90 ± 0.05	0.63 ± 0.10	0.89 ± 0.03
	1000	1.07 ± 0.04	0.89 ± 0.06	0.62 ± 0.10	0.89 ± 0.03
29.99	10	1.07 ± 0.04	0.87 ± 0.01	0.62 ± 0.11	0.90 ± 0.03
	25	1.07 ± 0.04	0.88 ± 0.02	0.61 ± 0.10	0.89 ± 0.03
	50	1.07 ± 0.04	0.87 ± 0.06	0.61 ± 0.11	0.89 ± 0.03
	100	1.07 ± 0.04	0.88 ± 0.05	0.61 ± 0.11	0.89 ± 0.03
	250	1.07 ± 0.04	0.89 ± 0.05	0.61 ± 0.11	0.89 ± 0.03
	500	$1.07 + 0.04$	$0.91 + 0.05$	$0.62 + 0.10$	$0.89 + 0.03$
	1000	1.07 ± 0.04	0.90 ± 0.05	0.62 ± 0.10	0.89 ± 0.03
34.63	10	1.07 ± 0.03	0.95 ± 0.01	0.65 ± 0.07	0.90 ± 0.02
	25	$1.07 + 0.04$	$0.92 + 0.02$	$0.64 + 0.08$	$0.90 + 0.03$
	50	1.07 ± 0.05	0.92 ± 0.02	0.63 ± 0.10	0.89 ± 0.04
	100	1.08 ± 0.05	0.92 ± 0.02	0.63 ± 0.10	0.89 ± 0.04
	250	1.07 ± 0.05	0.92 ± 0.02	0.63 ± 0.10	0.89 ± 0.04
	500	1.07 ± 0.04	0.92 ± 0.02	0.63 ± 0.10	0.89 ± 0.03
	1000	1.07 ± 0.04	0.92 ± 0.02	0.63 ± 0.10	0.89 ± 0.03
40.13	10	1.06 ± 0.03	0.92 ± 0.01	0.66 ± 0.08	0.89 ± 0.02
	25	1.06 ± 0.03	0.93 ± 0.01	0.66 ± 0.10	0.90 ± 0.02
	50				
	100	1.07 ± 0.04	0.92 ± 0.02	0.64 ± 0.10	0.89 ± 0.03
	250	1.07 ± 0.04	0.93 ± 0.02	0.65 ± 0.11	0.89 ± 0.03
	500	1.07 ± 0.04	0.93 ± 0.02	0.66 ± 0.10	0.90 ± 0.03
	1000	1.07 ± 0.04	0.93 ± 0.02	0.65 ± 0.10	0.89 ± 0.03
	10	1.07 ± 0.04	0.93 ± 0.02	0.65 ± 0.10	0.89 ± 0.03
61.70		1.08 ± 0.05	0.90 ± 0.02	0.62 ± 0.10	0.84 ± 0.04
	25	1.08 ± 0.04	0.89 ± 0.03	0.61 ± 0.09	0.85 ± 0.03
	50	1.08 ± 0.04	0.89 ± 0.03	0.60 ± 0.09	0.85 ± 0.04
	100	1.08 ± 0.04	0.91 ± 0.03	0.62 ± 0.10	0.86 ± 0.04
	250	1.09 ± 0.05	0.91 ± 0.03	0.60 ± 0.10	0.86 ± 0.04
	500	1.09 ± 0.05	0.92 ± 0.03	0.60 ± 0.10	0.86 ± 0.04
	1000	1.09 ± 0.05	0.92 ± 0.02	0.60 ± 0.11	0.86 ± 0.04
100.1	10	1.05 ± 0.04	0.95 ± 0.02	0.72 ± 0.11	0.88 ± 0.03
	25	1.06 ± 0.04	0.95 ± 0.02	0.70 ± 0.10	0.88 ± 0.03
	50	1.07 ± 0.04	0.95 ± 0.01	0.67 ± 0.10	0.87 ± 0.03
	100	1.07 ± 0.04	0.94 ± 0.02	0.66 ± 0.10	0.87 ± 0.03
	250	1.07 ± 0.04	0.94 ± 0.02	0.66 ± 0.10	0.86 ± 0.03
	500	1.07 ± 0.04	0.94 ± 0.02	0.65 ± 0.10	0.86 ± 0.03
	1000	1.08 ± 0.05	0.94 ± 0.02	0.64 ± 0.10	0.86 ± 0.04

Minimum number of pellets to be counted to achieve a result representative for the pellet batch^a

^a n.s., Analysis of variance did not identify any difference between the counts.

of the magnification, light intensity and calibration, the best threshold value was determined as already described and used for all other pellets.

3.2. *The influence of magnification and number of pellets to be counted*

The influence of the magnification and number of pellets was studied using pellet batches GR and AL. Seven different magnifications were used, corresponding to pixel heights between 20 and 100 mm. In total, 1000 pellets were counted for each batch. These were randomly drawn from the pellet bulk. The results for the different shape factors are summarised in Tables 2 and 3.

Analysis of variance was employed to determine the minimum number of pellets to be counted to obtain a shape factor value representative for the whole batch of pellets. The different numbers of pellets for which an arithmetic mean and standard deviation had been calculated were used as classification criterion into samples in the statistical analyses. When the global *F*-value indicated a significant difference between the samples, multiple pair comparisons (Bonferroni) between consecutive samples were carried out. Thus, class 1 (10 pellets counted) was compared with class 2 (25 pellets counted), class 2 with class 3, class 3 with class 4, etc. When a set of consecutive multiple pair comparisons up to the last sample (1000

pellets counted) did not indicate a statistically significant difference between the classes, the minimum number of pellets was set equal to the number of pellets counted in the class with the lowest label of this set of multiple pair comparisons. The minimum number of pellets to be counted for the two pellet batches and different magnifications used are compared in Table 4 for the different shape factors.

The first observation that can be made from Table 4 is that the assessment of different shape factors apparently requires different numbers of pellets to be counted. The value of the aspect ratio is least dependent on the number of pellets counted. However, the aspect ratio is also the shape factor that is least sensitive to pellet shape variability (Podczeck and Newton, 1994; Eriksson et al., 1997). This could explain the apparent insensitivity of this shape factor to the number of pellets counted. However, the shape factor e_R , which is highly sensitive to small variations is pellet shape, also appears only slightly dependent on the number of pellets counted. On the other hand, the circularity, which is as insensitive as the aspect ratio in defining shape, appears to depend critically on the number of pellets counted. As already discussed, the two-dimensional outlines of the pellets are reproduced from a set of squares, and all parameters depending on this type of image recognition (e.g. area, perimeter) are more

Table 4

likely to be variable in their values. The circularity is based on the area and the squared value of the perimeter of the particle outline (see Eq. (1)). The findings suggest that the error in image recognition can affect strongly the applicability of a shape factor. The circularity would appear, therefore, least suitable for the description of pellet shape employing image analysis.

The second observation that can be made from Table 4 is that there appears to be a trend towards higher numbers of pellets necessary to be counted if the magnification decreases. A pixel height of more than 35 um appears to be critical, but here the particle size has also to be considered. To identify the minimum magnification, i.e. the maximum pixel height (μm) , the particle size

Fig. 1. Pellet size (Feret diameter) as a function of the magnification and number of pellets counted for pellet batches AL (a) and GR (b) (not all magnifications tested are shown for better visibility). Magnifications (in pixel heights): \bullet , 20 μ m; \blacksquare , 30 μ m; \blacklozenge , 35 μ m; \blacktriangle , 40 μ m; ∇ , 60 μ m.

measured (Feret diameter) is drawn as a function of number of pellets and pixel height chosen (Fig. 1a,b). Although the pellets had been size classified, it is obvious that there is some size variation in each pellet batch. However, in most cases, the mean particle size approached a constant value after measurement of 100 pellets. Thus, if not only the particle shape but also the pellet size is a target of the image analysis, a minimum of 100 pellets should be counted. For pellet batch AL (Fig. 1a), the mean Feret diameter of 100 or more pellets counted is similar for the three largest magnifications tested (pixel heights, 20 , 25 and $30 \mu m$). However, a further reduction in magnification (pixel height, $35 \mu m$) leads to clearly smaller values for the Feret diameter, which is assumed to be flawed. Also, the magnitude of the Feret diameter obtained appears to fluctuate for magnifications with larger pixel heights than $30 \mu m$. A similar picture can be seen for batch GR (Fig. 1b). Hence, the minimum magnification, i.e. maximum pixel height, should not exceed 30 um for reliable pellet size results.

3.3. *Methodical error*, *reproducibility and repeatability of pellet shape measurements*

The methodical error and reproducibility of the pellet shape measurements were tested using a pixel height of $30 \mu m$. Five hundred pellets were chosen randomly from the pellet bulk. Their particle shape was evaluated five times in random order of the pellets, and the arithmetic mean and standard deviation of each measurement were calculated. All three pellet batches were included into the investigation. Table 5 summarises the results.

A method gives reproducible results if a statistical test procedure is unable to detect significant differences between replicated measurements. Hence, Analysis of variance was employed to test for significant differences between the five replicates. The shape factor chosen can be seen to influence the results. For the circularity, analysis of variance showed significant differences between the replicates for all pellet batches. Thus, in terms of circularity, the reproducibility appears unacceptable. However, the coefficient of variation between the five arithmetic mean values is in all

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Shape factor **Parameter Count GR** AL CY Aspect ratio 1.09 \pm 0.06 1.07 \pm 0.04 1.84 \pm 0.49 2 1.09 \pm 0.06 1.07 \pm 0.04 1.84 \pm 0.50 3 $1.09 + 0.05$ $1.07 + 0.04$ $1.84 + 0.53$ 4 1.09 ± 0.06 1.07 ± 0.04 1.85 ± 0.52 5 1.09 \pm 0.06 1.07 \pm 0.04 1.83 \pm 0.50 Mean based average 1.09 ± 0.00 1.07 ± 0.00 1.84 ± 0.01 Coefficient of variation 0.21% 0.15% 0.35% 0.35% *F*-value 1.00 1.00 1.00 Different counts None None None None None Circularity 1 0.83 \pm 0.04 0.85 \pm 0.03 0.65 \pm 0.08 2 0.84 \pm 0.04 0.85 \pm 0.03 0.67 \pm 0.08 3 0.83 ± 0.04 0.85 ± 0.03 0.67 ± 0.08
4 $0.83 + 0.04$ $0.85 + 0.03$ $0.66 + 0.08$ $0.83 + 0.04$ $0.85 + 0.03$ 5 0.83 \pm 0.04 0.85 \pm 0.03 0.67 \pm 0.08 Mean based average 0.83 ± 0.01 0.85 ± 0.00 0.66 ± 0.01
Coefficient of variation 0.89% 0.35% 1.39% Coefficient of variation 0.89% 0.35% *F*-value 15.26 4.05 7.27 Different counts 2^{*} None 1^{*} e_R 1 0.56 \pm 0.11 0.60 \pm 0.10 0.14 \pm 0.11 2 0.57 ± 0.12 0.61 ± 0.10 0.13 ± 0.11
3 $0.56 + 0.10$ $0.60 + 0.10$ $0.14 + 0.11$ $0.56 + 0.10$ $0.60 + 0.10$ $0.14 + 0.11$ 4 0.55 ± 0.11 0.60 ± 0.10 0.14 ± 0.11 5 0.55 ± 0.11 0.61 ± 0.10 0.14 ± 0.11
 0.56 ± 0.01 0.60 ± 0.00 0.14 ± 0.01 Mean based average 0.56 ± 0.01

Projection sphericity 1 0.86 ± 0.04 0.88 ± 0.03 0.52 ± 0.11
2 0.86 ± 0.04 0.89 ± 0.03 0.52 ± 0.11

Coefficient of variation 1.27% 0.39% 4.34% *F*-value 1.55 2.17 1.00 1.55 Different counts 2^{*} None None None

Mean based average 0.86 ± 0.00 0.89 ± 0.00 0.52 ± 0.01 Coefficient of variation 0.26% 0.10% 1.15% *F*-value 1.41 1.00 1.53 Different counts None None None

3 0.86 \pm 0.04 0.88 \pm 0.03

* Batch provided statistically significant difference in shape factor value.

cases below 1.5%, indicating a rather small overall methodical error. Hence, the lack of reproducibility is not due to a large methodical error, but presumably a result of the influence of the image recognition problems already discussed on this particular shape factor. The aspect ratio is a highly reproducible shape factor with a very low methodical error (coefficient of variation below 0.5% in all cases). Shape factor e_R and the projection sphericity are also fairly reproducible, although some statistically significant differences between replicates were found. The projection sphericity also shows a comparative low methodical error, which is highest for the cylindrical pellet batch (1.15%; Table 5). The methodical error for e_R depends strongly on gross changes in particle shape. For the pellet batch CY, which provides the other extreme to sphericity in the pellet shape,

 $\begin{array}{lll} 0.86 \pm 0.04 & 0.89 \pm 0.03 & 0.52 \pm 0.11 \\ 0.86 \pm 0.04 & 0.88 \pm 0.03 & 0.52 \pm 0.11 \end{array}$

4 0.86 \pm 0.04 0.89 \pm 0.03 0.52 \pm 0.11 5 0.85 \pm 0.04 0.89 \pm 0.03 0.51 \pm 0.11 the methodical error reached more than 4%. This could be caused by the random orientation of the pellets in the view field of the image camera.

The repeatability of the experiments is here defined as the variability between shape factor results obtained from five different sets of pellets. Each set consisted of 500 pellets randomly drawn from the pellet bulk. All other experimental conditions were the same as for the assessment of the methodical error already described. The results are listed in Table 6.

The repeatability appears linked to the pellet shape. For the batch that approached sphericity most closely, i.e. batch AL, analysis of variance could not identify a statistically significant difference between the five measurements for aspect ratio and e_R . The coefficient of variation between the arithmetic mean shape factor values was also

Table 6

Assessment of the repeatability of pellet shape measurements using image analysis

Shape factor	Parameter	Set	GR	AL	CY
Aspect ratio		1	1.09 ± 0.06	1.07 ± 0.04	1.84 ± 0.49
		\overline{c}	1.10 ± 0.06	1.08 ± 0.04	1.79 ± 0.54
		3	1.09 ± 0.05	1.07 ± 0.04	1.82 ± 0.42
		$\overline{\mathbf{4}}$	1.09 ± 0.05	1.07 ± 0.04	1.75 ± 0.49
		5	$1.09 + 0.05$	1.07 ± 0.04	1.75 ± 0.49
	Mean based average		$1.09 + 0.01$	1.07 ± 0.00	1.79 ± 0.04
	Coefficient of variation		0.53%	0.19%	2.21%
	F -value		5.62	1.23	3.25
	Different counts		$3*$	None	$1,3*$
Circularity		$\mathbf{1}$	$0.83 + 0.04$	0.85 ± 0.03	0.65 ± 0.08
		\overline{c}	0.85 ± 0.04	0.86 ± 0.03	0.67 ± 0.08
		3	0.86 ± 0.04	0.86 ± 0.03	0.67 ± 0.08
		4	0.86 ± 0.03	0.84 ± 0.04	0.66 ± 0.08
		5	0.85 ± 0.05	0.82 ± 0.06	0.66 ± 0.08
	Mean based average		0.85 ± 0.01	0.84 ± 0.02	0.66 ± 0.01
	Coefficient of variation		1.42%	1.87%	1.68%
	F -value		42.50	77.10	9.67
	Different counts		$1,2*$	$1,2,4,5*$	$1*$
e_{R}		$\mathbf{1}$	0.56 ± 0.11	0.60 ± 0.10	0.14 ± 0.11
		\overline{c}	0.55 ± 0.12	0.60 ± 0.10	0.16 ± 0.12
		3	0.59 ± 0.11	0.60 ± 0.10	0.14 ± 0.11
		4	0.57 ± 0.10	0.60 ± 0.10	0.16 ± 0.11
		5	0.57 ± 0.11	0.59 ± 0.10	0.16 ± 0.12
	Mean based average		0.57 ± 0.01	0.60 ± 0.01	0.15 ± 0.01
	Coefficient of variation		2.20%	1.60%	7.37%
	F -value		7.11	1.46	8.56
	Different counts		$3*$	None	$1,3*$
Projection sphericity		1	0.86 ± 0.04	0.88 ± 0.03	0.52 ± 0.11
		\overline{c}	0.85 ± 0.04	0.88 ± 0.03	0.54 ± 0.11
		3	0.86 ± 0.04	0.88 ± 0.03	0.52 ± 0.10
		$\overline{\mathcal{L}}$	0.86 ± 0.04	0.88 ± 0.03	0.53 ± 0.12
		5	0.86 ± 0.04	0.88 ± 0.03	0.53 ± 0.12
	Mean based average		0.86 ± 0.00	0.88 ± 0.00	0.52 ± 0.01
	Coefficient of variation		0.50%	0.30%	1.48%
	F -value		5.72	3.32	2.41
	Different counts		$3*$	None	None

* Batch provided statistically significant difference in shape factor value.

comparatively small (below 2% for all four shape factors tested). For batch GR, analysis of variance identified significant differences between the five measurements for all shape factors, and the coefficients of variation are also slightly higher. Unexpectedly, the differences in the analysis of variance for the five measurements using batch CY are not much more drastic than for batch GR. Also, the coefficients of variation except for e_R are in the same order of magnitude as for GR. The coefficient of variation for e_R is larger than 7%. Again, the random orientation of the pellets in the field of view might have influenced the value of this shape factor.

3.4. *Influence of light technique on pellet size and shape*

The influence of the light technique on the pellet characteristics was investigated using pellet batches GR and AL. Five hundred pellets were randomly drawn from each batch. For 100 of these pellets, the particle size (Feret diameter) was measured microscopically. The microscopic pellet size $(1176 + 104$ and $1300 + 81$ µm for batches GR and AL, respectively) is here regarded as the correct pellet size, i.e. the Feret diameter which should have been found using image analysis. Image analysis was performed: (a) as before, i.e. using top light; (b) positioning the light beams sidewise over the pellets in an angle of 45° to the top light position; and (c) using a light table. The results are listed in Table 7.

Apparently, there is a trend of the pellet size to increase from light position (a) to (c). Also, the pellets appear to be more round using a light table, especially when comparing aspect ratio and e_R . However, it had been discussed previously that the formation of shadows could influence the shape factor results (Podczeck and Newton, 1995). Top light produces white images on a black background and black shadows, whereas a light table produces black images against a bright background and dark shadows. Hence, in the latter case, it will be more difficult to set the correct threshold value, because the grey values for the pellets and the shadows are similar.

To identify the light position, which gives correct values, the Feret diameters of the image analyses can be compared with the equivalent microscopic values. A *t*-test was employed to statistically secure the findings. The *t*-values in the order of (a) to (c) are 1.26, 1.75 and 7.73 for batch GR, and 1.45, 1.19 and 6.50 for batch AL. In all cases, the limiting *t*-value ($P = 0.05$) is 1.96. Hence, light positions (a) and (b) are suitable for the assessment of pellet size and shape using image analysis. However, the use of a light table produces significantly too large pellet size values. Assuming that this is due to shadow formation, it must also be concluded that all shape factor values are wrong under these light conditions.

3.5. Considerations about limiting values for *shape factors*

Pellet characteristics determined using image analysis will always contain some inherent error. Some of the problems involved have been discussed in the introduction, some aspects have already been investigated, and a variety of other possible sources for erroneous measurements have been studied by Zingerman et al. (1992) and by Lindner and Kleinebudde (1993). It therefore appears necessary to consider practical limitations for the shape factors used.

It can be assumed that steel ball bearings are practically spherical. Hence, steel ball bearings of 1.0 mm diameter (Stefko Co. Ltd., Luton, UK) were used to assess limiting values for the individual shape factors. Unfortunately, steel ball bearings reflect any light considerably, so that their surface had to be treated before use in this experiment. Thus, they were carefully spayed with a black paint and rolled to avoid gross changes in particle shape due to uneven coat formation. Eight such ball bearings could be prepared. As before, top light was used, but a white background was employed. This resulted in black shadows, which could have disturbed the measurements. However, the CCD camera used is infrared sensitive, and the black paint had a 10 U lower grey value than the shadows formed. The image analyser used can distinguish objects if their image varies by two grey shades. Thus, also

 $a \bar{x}$, arithmetic mean value; s, standard deviation.

for these model spheres, a correct threshold value could be determined.

The different shape factors obtained for the eight pellets are listed in Table 8, as are the arithmetic mean values, standard deviations and coefficients of variations. From the results, it can be concluded that practically spherical two-dimensional images of pellets would have an aspect ratio value equal to or below 1.02, a circularity value above 0.93, and a projection sphericity value above 0.94. The value for the shape factor e_R , which has also a theoretical value of 1.0, appears with a practical sphericity limit of 0.8 rather small. However, it should be remembered that the strength of this shape factor is its sensitiv-

ity to very small deviations in shape, which are not discovered using the aspect ratio or circularity (Podczeck and Newton, 1994).

In practice, pellets are rarely ideally spherical, so it cannot be expected that a pellet batch will meet the afore-mentioned limiting values. A suitable reduction or increase (aspect ratio) has therefore to be considered. Here, however, the opinions of some authors appear questionable. For example, Baert et al. (1992, 1993a,b), Vervaet and Remon (1996), and Vervaet et al. (1994) define pellets with an aspect ratio equal or smaller than 1.2 as sufficiently round. Hellén and Yliruusi (1993) considered pellets with an aspect ratio up to 1.55 still as round. Hileman et al. (1997) quotes

 $a \bar{x}$, arithmetic mean value; s, standard deviation.

Fig. 2. Comparison between a circular and two elliptical two-dimensional particle outlines. AR, aspect ratio; *C*, circularity.

a reciprocal value of the circularity of 1.2 as a limiting value for acceptable roundness. This value is equivalent to a circularity of 0.83 as defined in Eq. (1). The circularity value accepted as round by Hellén and Yliruusi (1993) is 0.88 and above, while Wan et al. (1993) consider only values above 0.93. In Fig. 2, an ideal spherical image (i.e. circle) is compared with elliptical images of an aspect ratio of 1.2 and a circularity of 0.9. Clearly, pellets with a circularity value of just 0.9 are not even nearly round. Thus, the values considered by Hileman et al. (1997) and by Hellén and Yliruusi (1993) as limiting values for pellets to be considered round appear out of place. An aspect ratio of 1.2 appears a better solution and, for some applications, also has a practical value (Chopra et al., 1998). Assuming an absence of surface irregularities, which could add to the effect of aspect ratio on the value of the shape factor e_R , an aspect ratio of 1.2 is equivalent to an

 e_R value of about 0.48. However, pellets with an e_R value above 0.6 can readily be made (Sousa et al., 1996; Chopra et al., 1998). This in turn translates into an aspect ratio of 1.08 in the absence of surface irregularities. Hence, the limiting value for the aspect ratio should be reduced to 1.1, while 0.6 appears to be acceptable as the lower limiting value for e_{R} .

4. Conclusions

When image analysis is used to determine the size and/or shape of pellets, the illumination technique employed has to be considered as a main influence factor, which can lead to false values. The position of the light source is particularly crucial in providing an accurate particle size value. Top light is recommended, as here it gave a mean pellet size similar to the true pellet size. The use of a light table, however, produced significantly larger pellet size values.

A minimum pixel resolution appears necessary for an accurate shape parameter definition. One pixel should not cover more than 30 μ m for pellets of an average particle size of 1.2 mm. Shape descriptors, which are based on a multiple combination of area and perimeter data such as the circularity, are greatly dependent on the number of pellets counted. Shape factors, which do not (aspect ratio) or only as a single value do involve an area or perimeter measurement $(e_R,$ projection sphericity) are, however, nearly independent of the number of pellets counted, as long as the magnification is sufficiently large and the pellets are randomly drawn from the batch.

For nearly spherical particles, the methodical error to assess the various shape factors is below 1%, but for elongated particles, this error can reach 5%. The repeatability is also very good for nearly spherical particles $(2%), but increases to$ very large values if the particles are clearly elongated.

The limiting values for the various shape factors should be reconsidered. An upper value for the aspect ratio of 1.1 and a lower value of 0.6 for e_B are recommended. The circularity should not be used as shape factor to characterise spheres, because errors in image recognition can affect strongly the applicability of this shape factor. The projection sphericity has only a limited sensitivity to variations in particle shape.

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References

- Allen, T., 1997. Particle Size Measurement, 5th ed. Chapman & Hall, London pp. 128–137.
- Baert, L., Fanara, D., Remon, J.P., Massart, D., 1992. Correlation of extrusion forces, raw materials and sphere characteristics. J. Pharm. Pharmacol. 44, 676–678.
- Baert, L., Remon, J.P., Elbers, J.A.C., Van Bommel, E.M.G., 1993a. Comparison between a gravity feed extruder and a twin screw extruder. Int. J. Pharm. 99, 7–12.
- Baert, L., Vermeersch, H., Remon, J.P., Smeyers–Verbeke, J., Massart, D.L., 1993b. Study of parameters important in the spheronisation process. Int. J. Pharm. 96, 225–229.
- Chopra, R., Podczeck, F., Newton, J.M., 1998. The influence of shape and surface roughness on the filling performance of pellets into hard gelatine capsules. Proceedings of the 2nd World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, Paris, pp. 161–162.
- Cox, E.P., 1927. A method of assigning numerical and percentage values to the degree of roundness. J. Paleontol. 1, 179–183.
- Eriksson, M., Alderborn, G., Nyström, C., Podczeck, F., Newton, J.M., 1997. Comparison between and evaluation of some methods for the assessment of the sphericity of pellets. Int. J. Pharm. 148, 149–154.
- Hausner, H.H., 1966. Characterization of the powder particle shape. Planseeber. Pulvermet. 14, 75–84.
- Hawkins, A.E., 1993. The Shape of Powder–Particle Outlines. Research Studies Press Ltd, Taunton, UK, pp. 31– 33.
- Hellén, L., Yliruusi, J., 1993. Process variables of instant granulator and spheroniser: III. Shape and shape distributions of pellets. Int. J. Pharm. 96, 217–223.
- Hileman, G.A., Upadrashta, S.M., Neau, S.H., 1997. Drug solubility effects on predicting optimum conditions for extrusion and spheronization of pellets. Pharm. Dev. Technol. 2, 43–52.
- Lindner, H., Kleinebudde, P., 1993. Anwendung der automatischen bildanalyse zur charakterisierung von pellets. Pharm. Ind. 55, 694–701.
- Lundqvist, Å.E.K., Podczeck, F., Newton, J.M., 1997. The influence of disintegrant type and proportion on the properties of tablets produced from mixtures of pellets. Int. J. Pharm. 147, 95–107.
- Lundqvist, A.E.K., Podczeck, F., Newton, J.M., 1998. Compaction of and drug release from coated drug pellets mixed with other pellets. Eur. J. Pharm. Biopharm. 46, 369–379.
- McCarthy, C.J., 1976. Recent advances in the characterization of particulates using automatic evaluation of shape descriptors. Microstruct. Sci. 4, 339–346.
- Pentland, A., 1927. A method of measuring the angularity of sands. Proceedings and Transactions of the Royal Society of Canada, Vol. 21.
- Podczeck, F., Newton, J.M., 1994. A shape factor to characterize the quality of spheroids. J. Pharm. Pharmacol. 46, 82–85.
- Podczeck, F., Newton, J.M., 1995. The evaluation of a threedimensional shape factor for the quantitative assessment of the sphericity and surface roughness of pellets. Int. J. Pharm. 124, 253–259.
- Riley, N.A., 1941. Projection sphericity. J. Sediment. Petrol. 11, 94–97.
- Salako, M., Podczeck, F., Newton, J.M., 1998. Investigations into the deformability and tensile strength of pellets. Int. J. Pharm. 168, 49–57.
- Schneiderhöhn, P., 1954. Eine vergleichende studie über methoden zur quantitativen bestimmung von abrundung und form an sandkörnern. Heidelb. Beitr. Miner. Petrogr. 4, 172–191.
- Snedecor, G.W., Cochran, W.G., 1980. Statistical Methods, 7th edn. Iowa State University Press, Iowa, pp. 34–35.
- Sousa, J.J., Sousa, A., Podczeck, F., Newton, J.M., 1996. Influence of process conditions on drug release from pellets. Int. J. Pharm. 144, 159–169.
- Tsubaki, J., Jimbo, G., 1979. A proposed new characterization

of particle shape and its application. Powder Technol. 22, 161–169.

- Vervaet, C., Remon, J.P., 1996. Influence of impeller design, method of screen perforation and perforation geometry on the quality of pellets made by extrusion–spheronisation. Int. J. Pharm. 133, 29–37.
- Vervaet, C., Baert, L., Risha, P.A., Remon, J.P., 1994. The influence of the extrusion screen on pellet quality using an instrumented basket extruder. Int. J. Pharm. 107, 29–39.

Wan, L.S.C., Heng, P.W.S., Liew, C.V., 1993. Spheronization

conditions on spheroid shape and size. Int. J. Pharm. 96, 59–65.

- Yliruusi, J., Hellén, L., Muttonen, E., Merkku, P., Kristofferson, E., 1992. Mathematical modelling of image analysis data of pellets. Proceedings of the 11th Pharmaceutical Technology Conference, Vol. 3, Manchester, pp. 53–62.
- Zingerman, J.P., Mehta, S.C., Salter, J.M., Radebaugh, G.W., 1992. Validation of a computerized image analysis system for particle size determination. Pharmaceutical applications. Int. J. Pharm. 88, 303–312.